

REMARKS

Claims 1-7, 10, and 12-23 were pending in the present application. Claims 1, 3, 10, 12-19, and 21-23 have been canceled herein without prejudice to their presentation in another application. Claims 2, 4, 5, and 7 have been amended herein, support for which can be found in the original claims. No new matter has been added. Upon entry of the present amendment, claims 2, 4-7, and 20 will remain pending. **Because the amendments to the claims remove issues for appeal (i.e., enablement), Applicants respectfully request that they be entered into the record. See, M.P.E.P. §714.12.**

I. The Claimed Invention Is Not Obvious

Claims 1-7 and 20 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Stevenson et. al., J. Med. Chem., 1998, 41, 4623-4635 (hereinafter the “Stevenson reference”), in view of Bernstein et al., Bioorg. Med. Chem. Lett., 2001, 11, 2769-2773 (hereinafter the “Bernstein reference”). The Office asserts that one skilled in the art would have been motivated to modify compound 48 or 49 of the Stevenson reference by replacing the 2-methoxyphenyl group (from compound 48) or the 3,5-bis(trifluoromethyl)phenyl group (from compound 49) with the 3-cyanonaphthyl group of compound 4 of the Bernstein reference. Applicants traverse the rejection and respectfully request reconsideration because one skilled in the art would not have been motivated to modify the compounds reported in the Stevenson reference in view of the Bernstein reference in the manner suggested by the Office.

When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art). Indeed, consideration of the Stevenson and Bernstein references as a whole for what they each fairly suggest, demonstrates that a person of ordinary skill seeking to combine them would not have produced any claimed invention. In particular, one skilled in the art having examined both the

Stevenson reference and the Bernstein reference would have no motivation to remove the 2-methoxyphenyl group (from compound 48) or the 3,5-bis(trifluoromethyl)phenyl group (from compound 49) of the Stevenson compounds and replace it with the 3-cyanonaphthyl group from compound 4 of the Bernstein reference.

In a first aspect, the Stevenson reference reports that when the $-\text{CH}_2\text{-O-CH}_2-$ linker of compound 12 is replaced with a $-\text{CH}_2\text{-NH-CH}_2-$ linker to form compound 49, the $\text{hNK}_1 \text{ IC}_{50}$ increases from 0.95 ± 0.41 to 12.6 ± 8.8 . Thus, there is little, if any, motivation to use the $-\text{CH}_2\text{-NH-CH}_2-$ linker of compound 49.

Second, there is no motivation to further modify compound 49 of the Stevenson reference by replacing only the 3,5-bis(trifluoromethyl)phenyl group and replace it with the 3-cyanonaphthyl group from compound 4 of the Bernstein reference. Indeed, compound 4 of the Bernstein reference has many structural differences from compound 49 in the Stevenson reference -- it is not obvious to simply interchange portions thereof. Indeed, compound 4 reported in the Bernstein reference has a $-\text{CH}_2\text{-CH}_2\text{-CH(3,4-dichlorophenyl)-CH}_2\text{-N(CH}_3\text{)-C(=O)-}$ linker between the 3-cyanonaphthyl group and the piperidine group, whereas compound 49 of the Stevenson reference has a $-\text{CH}_2\text{-NH-CH}_2-$ linker between the 3,5-bis(trifluoromethyl)phenyl group and the piperidine group. Thus, these two linkers are quite different. Further, the piperidine groups of compound 49 of the Stevenson reference and compound 4 of the Bernstein reference also differ. For example, it is the distal carbon of the piperidine ring of compound 49 of the Stevenson reference that is attached to the linker discussed above, whereas it is the nitrogen of the piperidine ring of compound 4 of the Bernstein reference that is attached to its linker. In addition, the phenyl group that is attached to the piperidine group in compound 49 of the Stevenson reference is attached to the same carbon on the piperidine ring as the linker is attached, whereas the phenyl group (which is substituted by a methylsulfonyl group) that is attached to the piperidine group in compound 4 of the Bernstein reference is attached to the distal carbon on the piperidine ring, which is opposite to where the linker is attached. Thus, there are numerous differences between compound 49 of the Stevenson reference and compound 4 of the Bernstein reference such that it is not obvious to simply interchange portions thereof.

There is no teaching or suggestion in either of the two references for making the specific combination asserted by the Office. Indeed, one skilled in the art could retain the entire side chain portion of compound 4 (or variations thereof) of the Bernstein reference and replace the remainder of the compound with the corresponding portion of compound 49 of the Stevenson reference. Indeed, there are numerous ways to combine various portions of compound 49 of the Stevenson reference with various portions of compound 4 of the Bernstein reference -- but it is only upon examining Applicants' specification that one particular combination becomes apparent. Thus, the combination of references is improper for its use of hindsight reconstruction based upon Applicants' disclosure. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

Further, even if one skilled in the art combined the Stevenson and Bernstein references in the manner suggested by the Office, Applicants' claimed invention still does not result. Claim 2 recites that " R^4 and R^5 are, independently, selected from halogen, C_{1-4} alkoxy or halogenated C_{1-4} alkyl." In contrast, the corresponding positions of compound 49 of the Stevenson reference and compound 4 of the Bernstein reference are hydrogen.

Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

II. The Claimed Invention Is Sufficiently Enabled

Claims 10, 12-19, and 21-23 are rejected under 35 U.S.C. §112, first paragraph as allegedly failing to provide an enabling disclosure. Although Applicants disagree with the reasoning set forth in the Office Action, solely to advance prosecution of the present application, claims 10, 12-19, and 21-23 have been canceled herein without prejudice to their presentation in another application. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

III. Obviousness-Type Double Patenting

Claims 1-7, 10, 12-23 are provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-10 of co-pending Application No. 10/525,303 in view of the Stevenson reference. Applicants traverse this rejection and respectfully request reconsideration because the claimed subject matter is not an obvious variant.

The Office asserts that it would have been obvious to one of ordinary skill in the art to make Applicants' claimed compounds and then modify them as allegedly suggested by the Stevenson reference by adding the carbonyl group, thereby converting the amine to an amide (see, Final Rejection at pages 13 to 14). The Office asserts that "Stevenson suggests that compounds with an amino nitrogen that is too basic are less active. It goes without saying that the amino nitrogen is substantially more basic than an amide. In fact an amide is somewhat acidic" (see, Final Rejection at page 14).

An obviousness-type double patenting rejection is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. §103. *In re Braithwaite*, 154 U.S.P.Q. 29, 34 (C.C.P.A. 1967) and *In re Longi*, 225 U.S.P.Q. 645, 648 n.4 (Fed. Cir. 1985). Thus, under the law, the pivotal question in an obviousness-type double patenting analysis is: Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent? *In re Vogel*, 164 U.S.P.Q. 619 (C.C.P.A. 1970). If the answer to this question is no, there can be no double patenting. In making this analysis, then, the proper inquiry is as taught in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). See, M.P.E.P. §804.

Accordingly, the question to be answered in the present application is whether any claim in the present application defines merely an obvious variation of an invention disclosed and claimed in Applicants' co-pending Application No. 10/525,303. Thus, the John Deere inquiry begins with the compounds disclosed in Applicants' co-pending Application No. 10/525,303, and any alleged motivation to modify those compounds by the reports in the Stevenson reference to arrive at Applicants' presently claimed compounds. According to the Office's own reasoning, there is no motivation provided in the Stevenson reference for **removing** the carbonyl group from the compounds claimed in Applicants' co-pending Application No. 10/525,303, thus yielding them more basic (according to the Office), to arrive at Applicants'

presently claimed invention. Accordingly, Applicants respectfully request that the provisional obviousness-type double patenting rejection be withdrawn.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Office is invited to contact Applicants' undersigned representative at (610) 640-7859 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,

/Paul K. Legaard, Reg.# 38534/
Paul K. Legaard, Ph.D.

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Pepper Hamilton LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312-1183

Telephone: 610.640.7859
Facsimile: 267.430.7647